PROTEIN AND URIC ACID PATTERNS IN MALIGNANT DISEASE

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I INTRODUCTION

In an earlier, detailed study of 92 patients suffering from malignant disease and all receiving cytotoxic drugs, a number of interesting facts emerged.

Of these, two were considered of particular interest. It was noted that in 60% of the total cases the α-2-globulin fraction of the serum electrophoretic pattern was raised, often to a considerable degree. If the cases of locally advanced disease or those demonstrating metastases were alone considered, then the percentage showing a raised α-2-globulin fraction was 76. Secondly, it was found that the serum and urinary uric acid levels were frequently raised in malignant disease and could be further altered by treatment with cytotoxic drugs or radiotherapy.

During this original study I further became impressed by the lack of an objective means of determining tumour response to cytotoxins (or radiotherapy) at an early stage in the treatment.

The significance of these changes in the protein pattern and in the uric acid levels in plasma and urine is obscure and relatively scant attention has been given to these problems in clinical publications.

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It was known that changes occur in the globulin fraction of the plasma proteins in certain liver diseases. Gelhorn, in 1958, reported a greater agglutination of leucocytes of cancer patients than of those of normal patients by an antiserum prepared against the α-2 fraction of the serum.[1] No report, however, was made of the actual levels of α-2-globulin found in the serum of these patients.

In 37 cases of metastatic carcinomatosis Sunderman (1964) demonstrated a significant increase in the mean concentrations of α-1 and α-2 globulins in the electrophoretic fractions of the serum proteins.[2] He was of the opinion that these increases constituted a common and non-specific pattern which should not be regarded as evidence of neoplastic disease. No attempt was made to determine the significance of these findings, but the comment was made that these changes "might be of value in determining remissions".

Although a slightly different problem, it is of interest to note that Macbeth and his co-workers in Edmonton were able to demonstrate an elevation of the carbohydrate fraction of the plasma glycoproteins in patients and experimental animals harbouring malignant neoplasms. They commented that this elevation was not specific for malignant disease but was intimately related to the neoplastic process. They further drew attention to the lack of information concerning the significance of these findings.[3]

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It thus appears that, although a very considerable amount of work is in progress on such problems as the ultrastructure of malignant cells, the various aspects of nucleic acid synthesis and metabolism, and on the problem of immunity in malignancy, relatively little work has been done, at a clinical level, on the significance and potential value of the changing patterns of α-2-globulin in malignant disease.

Even less information is available on the changes which occur in uric acid levels in plasma and urine in malignancy, particularly after treatment with cytotoxic drugs. It was known that hyperuricaemia could be produced by radiotherapy, steroids, or cytotoxic drugs in leukaemia and reticulosis, and that on occasion hyperuricaemia may be sufficiently severe to cause acute renal failure[4]. The employment of serial uric acid determinations in plasma and urine as a means of assessing response to cytotoxic treatment of solid tumours has, however, not been reported.

It was therefore considered that by a detailed study of the changes in serum electrophoretic pattern, with particular reference to the α-2-globulin fraction, together with a simultaneous study of the changes in plasma and urinary uric acid levels before and after treatment with cytotoxic drugs, some diagnostic and prognostic significance might derive from the results obtained.

II AIMS/

II AIMS

The aims of the study may therefore be summarised as follows:-

(a) To obtain support for the concept that the α-2-globulin fraction of the serum electrophoretic pattern is frequently raised in malignant disease and may be of some diagnostic significance.

(b) To study the changes in the serum α-2-globulin and in the uric acid levels in plasma and urine before and after administration of cytotoxic drugs in order to obtain information of possible prognostic significance.

III METHOD

It was considered feasible to carry out the two parts of the study simultaneously. The total study was, however, planned in three phases.

Phase 1.- The study of a selected group of patients demonstrating advanced malignant disease and treated with cytotoxic drugs. This group of patients to be controlled against patients suffering from advanced inflammatory disease requiring operative treatment.

Phase/

Phase 2.- A clinical study of electrophoretic patterns and uric acid levels in all patients with malignant disease admitted to the Unit before and after surgery and whether receiving cytotoxins or not.

Phase 3.- A clinical and laboratory study of the part played by the breakdown of normal tissues in determining serum electrophoretic and uric acid patterns following treatment with cytotoxic drugs.

Each phase to occupy a period of 9-12 months; Phases 2 and 3 to depend in their final form on the outcome of the preceding phases, but to run, in part, concurrently.

This paper is a report of the results of Phase 1 which has occupied the 12-month period from April 1964 to date. At this stage the work remains incomplete and continues as part of the total study.

Two groups of patients were studied.

Group A - Patients with locally advanced tumours or with known metastases. Many of these patients had been submitted to operation and all received cytotoxic drugs.

Group B - Patients with advanced inflammatory disease, e.g. empyema of gallbladder, ulcerative colitis, Crohn's disease.

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Group/

Group A patients.- These patients were mostly admitted to a single surgical charge over a 12-month period, as stated above. Certain patients were, however, seen and treated in other units, and one patient remained throughout her course in a medical charge.

Group B patients.- The control group of patients were all admitted to a single surgical charge over the same 12-month period. They represent only a small proportion of the total patients admitted during this period and were studied concurrently with Group A patients wherever possible.

IV INVESTIGATIONS

In addition to the usual and routine investigations required by the patient's particular condition, all patients in the study had an initial estimation of plasma proteins, serum electrophoresis, and serum uric acid carried out. In 13 Group A patients and in 6 Group B patients the urine was tested quantitatively for uric acid.

An E.S.R. was carried out in all patients.

Further estimations of serum electrophoresis, uric acid, urinary uric acid and E.S.R. were made at intervals after operation or after administration of cytotoxic drugs.

The/

The method employed for serum electrophoresis was that described by Albert Recht and employed routinely in our biochemical laboratory.[5] Serum uric acid was determined by the modified method described by Eichhorn et al.[6] and the urine uric acid was estimated by the method of Folin and Macallum.[7]

It is considered throughout the study that changes in any particular pattern or level are of greater significance than individual levels.

The initial results and the changing results obtained following cytotoxic therapy constitute the basis of this phase of the study.

V CASE SUMMARIES

(a) Treated patients

CASE NO.- 1 INITIALS.- W.S. SEX.- M AGE.- 60

DIAGNOSIS.- Hypernephroma right kidney.

HISTORY.- Increasing pain in right groin for 5 months with intermittent haematuria.

Large hypernephroma removed on 28/2/64.

CYTOTOXIC TREATMENT.- Thiocolciran, 40 mg, by intravenous injection between 15/3/64 and 6/4/64.

PROGRESS.- Patient remains alive and free of evidence of recurrence.

POINTS OF INTEREST.- Typical presentation of hypernephroma. Cytotoxic drugs were exhibited as prophylactic measure. α-2-globulin raised initially and remaining elevated throughout. No uric acid levels available for this patient, and urine uric acid estimations were not carried out.

COMMENT.- Insufficient results for comment. Of interest because of raised α-2-globulin with small tumour.

CASE/

CASE NO.- 2 INITIALS.- W.E. SEX.- M AGE.- 81

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- Increasing dysphagia for 6 months, complete dysphagia for 2 weeks. Severe dyspepsia. Marked anorexia and weight loss.

CYTOTOXIC TREATMENT.- Thiocolciran, 350 mg, by intravenous injection, and methotrexate, 32.5 mg, orally in intermittent courses.

PROGRESS.- Complete disappearance of dysphagia within 10 days of commencing cytotoxic therapy with gain in health and improvement in general condition. Relapse after 3 months. Further 3 months' remission with second course of treatment. Mousseau-Barbin tube inserted through cardia 8 months after commencing treatment. Died 15/1/65.

POINTS OF INTEREST.- Advanced carcinoma of cardia, initially causing confusion with peptic oesophagitis and stricture formation because of severe pain. Good subjective response to treatment. α-2-globulin slightly raised initially. Elevation becoming marked shortly after commencing treatment, thereafter persisting at increased level. Serum uric acid results for this patient are not available and urine uric acid estimations were not carried out.

COMMENT.- Insufficient results are available to comment on tumour effect, but rising α-2-globulin suggests continued activity despite subjective improvement.

CASE NO.- 3 INITIALS.- A.M. SEX.- M AGE.- 54

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- Epigastric discomfort, nausea after meals, and loss of 7 lb in weight over 3 months.

Inoperable carcinoma of stomach at laparotomy on 10/3/64 (Western General Hospital).

CYTOTOXIC TREATMENT.- Thiocolciran, 650 mg intravenously, and methotrexate, 505 mg orally. Cyclophosphamide, 1200 mg intravenously.

PROGRESS.- Symptomatic control for 6 months and then rapid decline to death in the ward on 19/11/64. Post-mortem not requested.

POINTS OF INTEREST.- α-2-globulin normal initially and remaining normal until 6 months after treatment commenced when the level was significantly elevated and remained high. Serum uric acid remained normal throughout and no estimation of urine uric acid.

COMMENT.- Very doubtful if any significant effect of drugs on tumour breakdown although activity checked for 6 months.

CASE/

CASE NO.- 4 INITIALS.- J.McA. SEX.- F AGE.- 61

DIAGNOSIS.- Carcinoma of ovaries.

HISTORY.- Invasive epidermoid carcinoma of cervix found on cone ciopsy April 1964. At subsequent laparotomy on 6/5/64 found to have extensive malignant disease of both ovaries with widespread peritoneal metastases.

CYTOTOXIC TREATMENT.- Thiocolciran, 380 mg by intravenous injection; thiotepa, 22.5 mg intrapleurally; and cyclophosphamide, 600 mg orally.

PROGRESS.- Remained well for 2 months, developed pleural effusion uncontrolled despite treatment, and deteriorated rapidly to death at the end of October 1964.

POINTS OF INTEREST.- α-2-globulin normal initially and remaining normal throughout. Serum uric acid slightly raised initially and remaining high-normal throughout. No estimation of urine uric acid.

COMMENT.- Insufficient results obtained, but of interest from the point of view of silent tumour already advanced at diagnosis, with normal α-2- levels and probably no significant response to treatment.

CASE/

CASE NO.- 5 INITIALS.- M.O. SEX.- F AGE.- 45

DIAGNOSIS.- Carcinoma of breast.

HISTORY.- Stage III carcinoma of breast treated by radical mastectomy and radiotherapy in 1960.

Found to have rheumatic heart disease in 1962 and subsequently developed congestive cardiac failure in July 1964. Bilateral pleural effusions at that time thought either due to heart condition or to recurrent malignant disease.

Readmitted to medical unit January 1965 with ascites and massive intra-abdominal malignancy.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 1,400 mg, by intravenous infusion.

POINTS OF INTEREST.- Case of especial interest because results available at an early stage and at a point when doubt existed as to nature of pleural effusions. α-2-globulin raised initially and remaining very high throughout. Serum uric acid raised initially and remaining high throughout. No estimation of urine uric acid.

COMMENT.- Period of treatment short and no objective evidence of tumour effect.

CASE/

CASE NO.- 6 INITIALS.- A.P. SEX.- M AGE.- 63

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- Increasing lassitude, anorexia, loss of weight and left hypochondrial pain for 6 months. Diagnosed as inoperable carcinoma of stomach at laparotomy on 7/1/64.

Subtotal gastrectomy 1 year later (20/1/65).

CYTOTOXIC TREATMENT.- Thiocolciran, 580 mg by I.V.I. and methotrexate, 370 mg orally in 3 courses. Treatment continues.

PROGRESS.- Remains well with normal appetite, steady gain in weight and free of symptoms.

POINTS OF INTEREST.- Case of especial interest from point of view of "second-look" procedure. Gastrectomy successfully carried out 1 year after an operative diagnosis of inoperable malignant disease of stomach. Serum proteins not estimated at initial operation (before commencing present programme). α_2-globulin was raised at first estimation in June 1964 and remains elevated. Uric acid, initially high, has fallen progressively since and remains low. Urine uric acid estimations within normal range on occasions estimated.

COMMENT.- Results suggest only a minimal effect on tumour breakdown despite apparent subjective control for a year, but activity possibly checked during this period. Case illustrates difficulty of estimating such factors as operability and clinical response to cytotoxins.

CASE NO.- 7 INITIALS.- J.C. SEX.- M AGE.- 58

DIAGNOSIS.- Hypernephroma.

HISTORY.- Right nephrectomy for an extensive hypernephroma 13/11/62. Incomplete excision.

Free of recurrence until 3/10/63 when reappeared with large mass in right loin. Mass slowly increased in size, producing severe local pain, with pain and paraesthesiae in right leg.

One week's palliative radiotherapy to mass 13/5/64 with improvement in leg symptoms, but no effect on pain.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 7,200 mg by intravenous injection and orally.

PROGRESS.- Moderate relief of abdominal pain but recurrence of leg symptoms. Gradual deterioration in general condition and died at home 25/8/64.

POINTS OF INTEREST.- Massive recurrence of hypernephroma with pulmonary spread and severe pain. α-2-globulin raised initially and remaining high throughout. Serum uric acid initially high, falling rapidly after treatment and remaining low. Urine uric acid high initially, remaining high but falling after treatment.

COMMENT.- Results suggest no appreciable effect on tumour breakdown but possibly some slowing of activity for a short time.

CASE NO.- 8 INITIALS.- E.H. SEX.- F AGE.- 60

DIAGNOSIS.- Carcinoma of ovaries. Widespread peritoneal and omental deposits.

HISTORY.- Progressive, painless abdominal distension for 1 week. At laparotomy on 7/7/64 found to have widespread malignant disease from ovarian primary.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 2,600 mg intravenously and 300 mg intrapleurally; thiotepa, 90 mg intraperitoneal and 60 mg intrapleural.

PROGRESS.- Control of malignant ascites and malignant pleural effusion obtained. Slowly developed an Addisonian state suggesting malignant replacement of adrenal glands. Died at home 16/11/64.

POINTS OF INTEREST.- Silent development of advanced ovarian malignancy. α-2-globulin slightly raised initially. Increase in α-2-globulin more marked after treatment and level remained high throughout. Uric acid initially low increasing after therapy and remaining at high-normal levels. No urine uric acid estimations carried out.

COMMENT.- These results suggest a moderate effect on tumour breakdown with apparent control of activity for 4 months.

CASE NO.- 9 INITIALS.- M.H. SEX.- F AGE.- 58

DIAGNOSIS.- Carcinoma of colon.

HISTORY.- Right hemicolectomy for carcinoma of colon 3/12/63. No other metastases noted at laparotomy.

In June 1964 developed severe pain in mid-thoracic spine; subsequently complained of double vision, unsteadiness of gait, anorexia, nausea, and weight loss.

CYTOTOXIC TREATMENT.- Thiocolciran, 60 mg, by intravenous injection; and methotrexate, 10 mg, orally.

PROGRESS.- Patient clinically demonstrating widespread metastases but proof of these was difficult to establish. α-2-globulin considerably raised and remaining raised. Uric acid normal and remaining normal.

COMMENT.- Too few results but probably no effect on tumour.

CASE NO.- 10 INITIALS.- S.O. SEX.- F AGE.- 62

DIAGNOSIS.- Carcinoma of breast.

HISTORY/

HISTORY.- Simple mastectomy and radiotherapy for Stage II carcinoma right breast 1947. Frequent skin recurrences treated by radiotherapy or excision, 1950-1964.

At review 29/7/64 complained of increasing breathlessness and tightness right side of chest. Large right-sided pleural effusion present; confirmed by cytology to be malignant.

CYTOTOXIC TREATMENT.- Thiotepa, 45 mg, by intrapleural instillation.

PROGRESS.- Remains well and free of symptoms.

POINTS OF INTEREST.- Very slowly growing malignancy demonstrating considerable "tumour-host resistance". α-2-globulin only very slightly raised, and pattern not changing with treatment. Uric acid normal and no increase in urinary excretion with treatment.

COMMENT.- Suggests overall effect of treatment on tumour is minimal despite prolonged symptomatic control.

CASE NO.- 11 INITIALS.- P.W. SEX.- M AGE.- 55

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- Gnawing epigastric pain, anorexia, and weight loss for 3 months.

Extensive irremoveable gastric carcinoma at laparotomy on 1/7/64.

CYTOTOXIC/

CYTOTOXIC TREATMENT.- Thiocolciran, 80 mg, by I.V.I.; and methotrexate, 100 mg, by mouth.

PROGRESS.- Developed severe buccal ulceration and marked bone marrow depression. Died at home 4/8/64.

POINTS OF INTEREST.- Typical carcinoma of stomach, severe side effects of cytotoxic therapy. α_2-globulin normal initially and remaining so. Uric acid low initially and only slightly increased during treatment. No estimation of urine uric acids carried out.

COMMENT.- Period of treatment too short and side effects of drugs too severe for assessment of tumour effect.

CASE NO.- 12 INITIALS.- M.G. SEX.- F AGE.- 57

DIAGNOSIS.- Astrocytoma. Grade III.

HISTORY.- Craniotomy and subtotal excision of a malignant astrocytoma of right temporal parietal region on 17/7/64 following a 3-month history of increasing headache and progressive disorientation.

CYTOTOXIC TREATMENT.- Epodyl, 7,500 mg, by intermittent intra-arterial injection/

injection (right internal carotid artery); thiocolciran, 480 mg, by intermittent intravenous injection; and methotrexate, 320 mg, orally.

PROGRESS.- 6 months of marked symptomatic relief with rapid decline and death, on 15/3/65 (Eastern General Hospital).

POINTS OF INTEREST.- Rapidly growing cerebral tumour. ∝-2-globulin raised initially, remaining slightly elevated throughout treatment, but no significant change in overall pattern. Uric acid normal initially, and remaining unchanged throughout. No estimation of urine uric acid was made.

COMMENT.- These results suggest very little influence on tumour despite subjective improvement. An alternative view is that the total bulk of tumour, even at death, was small. The content of purine derivatives in cerebral tumours is unknown and therefore the influence on uric acid excretion is unpredictable.

CASE NO.- 13 INITIALS.- T.H. SEX.- M AGE.- 58

DIAGNOSIS.- Carcinoma of stomach.

HISTORY/

HISTORY.- Progressive listlessness, anorexia, and loss of weight for 3 months.

Extensive infiltrating inoperable carcinoma of stomach at laparotomy 12/10/64. No operative procedure.

CYTOTOXIC TREATMENT.- Thiocolciran, 350 mg, intravenously; methotrexate, 390 mg, orally.

PROGRESS.- Transient buccal ulceration. General condition remained poor but 3 months after commencing treatment was eating reasonably well and free of pain. Deteriorated rapidly and died at home 15/1/65.

POINTS OF INTEREST.- Typical carcinoma of stomach. α_2-globulin considerably raised initially, remaining high throughout. Uric acid high initially and remaining high throughout. No estimation of urine uric acid.

COMMENT.- Results suggest possible objective response with continued tumour breakdown. Patient thought to have died of intercurrent infection.

CASE/

CASE NO.- 14 INITIALS.- E.L. SEX.- F AGE.- 48

DIAGNOSIS.- Carcinoma of pancreas.

HISTORY.- Progressive listlessness, anorexia, and vomiting for 6 months with epigastric discomfort for 3 weeks.

Inoperable carcinoma of pancreas at laparotomy 2/12/64. Palliative gastro-enterostomy.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 12,550 mg, by intravenous injection and orally.

PROGRESS.- Patient is alive and remains reasonably well. Has an enormous mass in abdomen but claims to be entirely free of pain and has only occasional vomiting.

POINTS OF INTEREST.- α-2-globulin raised initially, falling to normal levels within 2 weeks of starting treatment and subsequently increasing again. Serum uric acid initially normal and remaining normal. Urine uric acid raised initially; slight increase following treatment, and subsequent fall, but remaining raised.

COMMENT.- Very advanced tumour of head of pancreas. Difficult to assess significance of change in α-2-globulin pattern. Uric acid levels suggest minimal influence on tumour.

CASE/

CASE NO.- 15 INITIALS.- J.K. SEX.- M AGE.- 63

DIAGNOSIS.- Carcinoma of pancreas.

HISTORY.- Irremoveable carcinoma of head of pancreas at laparotomy on 6/3/62. Cholecyst-jejunostomy.

Reporting 17/11/64 with increasingly severe epigastric and back pain for 6 months associated with marked weight loss and severe steatorrhoea. Large mass palpable in epigastrium.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 5,650 mg, by intravenous infusion and orally.

PROGRESS.- Only minimal and transient relief of pain. No effect on steatorrhoea. Progressive deterioration to death at home on 12/1/65.

POINTS OF INTEREST.- No protein or uric acid estimations are available for initial admission in 1962. α_2-globulin significantly raised when reporting in November and remaining high. Uric acid normal and remaining so. Urine uric acid normal and not affected by treatment.

COMMENT.- No objective effect on tumour.

CASE/

CASE NO.- 16 INITIALS.- J.H. SEX.- M AGE.- 59

DIAGNOSIS.- Cerebral astrocytoma, Grade III.

HISTORY.- Inoperable Grade III astrocytoma of right parietal temporal region of brain at operation on 5/11/64 (Western General Hospital). Following operation remained drowsy, disorientated, and developed an enormous bulging over the decompressed area.

CYTOTOXIC TREATMENT.- Epodyl, 5,000 mg, by intra-arterial infusion; thiocolciran, 70 mg, by intravenous injection; cyclophosphamide, 700 mg, orally; and methotrexate, 35 mg, orally.

PROGRESS.- Rapid and remarkable improvement in general state and in central nervous signs, persisting for 5 weeks after treatment. Thereafter rapid decline to death at home at the end of January 1965.

POINTS OF INTEREST.- α_2-globulin raised initially and, although no evidence of metastases, remained high throughout. Serum uric acid normal and remaining normal throughout. No estimation of urine uric acid.

COMMENT.- Results suggest no objective response to treatment despite reasonable subjective response.

CASE/

CASE NO.- 17 INITIALS.- A.G. SEX.- M AGE.- 61

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- Progressive anorexia, weight loss and epigastric pain for 9 months. Chronic asthmatic.

Extensive inoperable carcinoma of stomach at laparotomy 16/11/64. No operative procedure.

CYTOTOXIC TREATMENT.- Thiocolciran, 400 mg, intravenously and methotrexate, 80 mg, orally. Treatment continues.

PROGRESS.- After initial period of increased symptoms has for 4 months been well with fair appetite, less pain, and steady weight.

POINTS OF INTEREST.- α-2-globulin significantly raised when first presented, remaining high but with one record of a normal level three months after commencing treatment; later levels again elevated. It is to be noted that previous medical notes record a normal α-2-globulin level despite chronic asthma. Serum uric acid level raised initially, remaining high. Urine uric acid high, remaining high after treatment.

COMMENT.- Results suggest slight but definite effect on tumour, correlating with good symptomatic response.

CASE/

CASE NO.- 18 INITIALS.- J.T. SEX.- M AGE.- 59

DIAGNOSIS.- Carcinoma of pancreas.

HISTORY.- Aching lower abdominal pain for 2 years, diabetes and steatorrhoea for 6 months.

Inoperable carcinoma head of pancreas at laparotomy 2/12/64. Extensive hepatic deposits. No operative procedure.

Palliative cholecyst-jejunostomy for obstructive jaundice 8/2/65.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 9,400 mg, intravenously, orally and intraperitoneally.

PROGRESS.- Initial dramatic relief of pain and steatorrhoea but of short duration. Massive increase in hepatic deposits with ascites. Died at home 18/4/65.

POINTS OF INTEREST.- α-2-globulin raised initially, remaining high throughout. Serum uric acid high initially, falling after treatment with one peak after second operation. Levels thereafter falling. Urine uric acid slightly raised initially with further slight rise following treatment.

COMMENT.- Results suggest no significant effect on tumour despite initial subjective improvement.

CASE/

CASE NO.- 19 INITIALS.- J.W. SEX.- M AGE.- 35

DIAGNOSIS.- Widespread carcinoma of unknown origin.

HISTORY.- 5-month history of increasingly severe pain in right lower chest and abdomen. Pain undiagnosed despite prolonged investigation in medical unit.

Diagnostic laparotomy 18/1/65 revealed widespread transperitoneal dissemination of carcinoma of unknown origin. Biopsy only. No operative procedure.

CYTOTOXIC TREATMENT.- Nitrogen mustard, 30 mg, by intravenous injection and cyclophosphamide, 2,400 mg, orally.

PROGRESS.- Almost complete but temporary remission of pain achieved with some regression of involved glands. Overall progression, however, of a rapidly disseminating carcinoma of which the primary site was never found. Died at home 22/3/65.

POINTS OF INTEREST.- α-2-globulin significantly raised initially and elevation becoming more marked throughout course of treatment. Serum uric acid level frequently estimated but never elevated. Urine uric acid levels slightly elevated and remaining unchanged throughout treatment.

COMMENT.- Results suggest no significant effect on tumour breakdown or activity.

CASE/

CASE NO.- 20 INITIALS.- J.G. SEX.- F AGE.- 53

DIAGNOSIS.- Carcinoma of pancreas.

HISTORY.- 3-month history of intermittent colicky abdominal pain, increasing constipation and general malaise.

Inoperable carcinoma of body and tail of pancreas with extensive omental and peritoneal and hepatic deposits proven at laparotomy on 14/10/64. No operative procedure carried out.

In January 1965 presented with constant severe incapacitating pain in abdomen and back. Confused and hallucinated.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 1,200 mg, by intravenous drip over 24 hours.

PROGRESS.- Rapid and dramatic relief of pain. Improvement in general condition. Able to sleep and no longer hallucinated. Died at home 3/3/65.

POINTS OF INTEREST.- Typical example of a carcinoma of body and tail of pancreas. No estimations of proteins or uric acid at initial admission. α-2-globulin considerably raised when patient re-presented with severe pain. Level increased steadily following treatment. Uric acid low initially and remaining low throughout. Urine uric acid slightly raised, moderate increase following treatment but again dropping fairly rapidly.

COMMENT/

COMMENT.- Results suggest minimal objective tumour response in addition to subjective improvement.

CASE NO.- 21 INITIALS.- M.K. SEX.- F AGE.- 52

DIAGNOSIS.- Carcinoma of breast.

HISTORY.- Radical mastectomy for Stage I carcinoma right breast August 1963.

Excision of local recurrence mastectomy scar January 1964 and removal of pre-malignant adenoma of rectum.

Further polyp excised from rectum and shown to be papillary carcinoma, February 1964. Further skin and axillary node recurrence between April and July 1964. Progressive skeletal and pulmonary metastases between September 1964 and January 1965. Skeletal metastases treated with symptomatic relief by radiotherapy. Increasing breathlessness and general malaise. Large right pleural effusion shown to be malignant on cytology.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 1,000 mg, by intrapleural instillation. Remains under treatment.

PROGRESS.- Symptomatically much improved, without repeated aspiration.

POINTS/

POINTS OF INTEREST.- No record of proteins or uric acids until brought into this programme. α_2-globulin normal initially and remaining so. Uric acid initially low, but rising to a high level immediately prior to treatment. Further increase following treatment with sustained high level. Urine uric acid initially normal, rising to significant peak before treatment commenced, falling following treatment, but remaining moderately elevated.

COMMENT.- Patient demonstrates widespread disease with possible objective response to treatment. Further results required.

CASE NO.- 22 INITIALS.- J.McI. SEX.- F AGE.- 54

DIAGNOSIS.- Metastatic malignant disease of unknown primary origin.

HISTORY.- Swelling in right groin for 6 weeks with increasingly severe pain in the region of D6. Clinically diagnosed as widespread malignant disease but the primary site could not be defined. Palliative radiotherapy to groin glands and dorsal spine, Dec.1964. Some relief of pain and reduction in size of glands.

Further metastases appearing and rapid general deterioration.

CYTOTOXIC/

CYTOTOXIC TREATMENT.- Cyclophosphamide, 1,800 mg, by intravenous drip and intravenous injection. Treatment continues.

PROGRESS.- Continued to run high grade pyrexia, but slow improvement in general condition.

POINTS OF INTEREST.- Rapidly spreading malignant disease with considerable systemic disturbance. α-2-globulin raised initially and remained high throughout treatment. Serum uric acid initially low but rising to above normal immediately prior to treatment and again decreasing following treatment. Urine uric acid output high on normal ward diet, rising 48 hours after treatment and falling again 2 weeks after treatment commenced.

COMMENT.- These results suggest very little effect on breakdown of the tumour but possibly indicate (by the falling uric acid level) some reduction in activity. This is, to some extent, supported by clinical progress.

CASE NO.- 23 INITIALS.- R.C. SEX.- M AGE.- 66

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- Increasing epigastric pain with vomiting after meals and loss of 2 st in weight over 6 months.

Inoperable carcinoma of stomach at laparotomy 23/3/65.

CYTOTOXIC/

CYTOTOXIC TREATMENT.- Thiocolciran, 120 mg, intravenously and methotrexate, 115 mg, orally. Treatment continues.

PROGRESS.- At last review was feeling well and beginning to eat normally. Pain decreasing.

POINTS OF INTEREST.- α-2-globulin normal initially, becoming elevated at last reading. Serum uric acid normal and remaining normal. No estimation of urine uric acid.

COMMENT.- Too early to make proper comment, but no evidence as yet of objective response.

CASE NO.- 24 INITIALS.- J.M. SEX.- M AGE.- 40

DIAGNOSIS.- Carcinoma of bronchus. Gross hepatic metastases.

HISTORY.- Intermittent bouts of sweating, dizziness and progressive weight loss for 3 months.

Laparotomy confirmed gross hepatic metastases.

CYTOTOXIC THERAPY.- Thiotepa, 75 mg, by intra-arterial (hepatic) injection. Hepato-renal failure and death on 14/4/65.

POINTS OF INTEREST.- Although this patient was not dealt with by myself and only a few results are available, it is interesting to note/

note a normal α_2-globulin despite gross liver involvement and a very high serum uric acid of 25.5 mg/100 ml 36 hours after administration of cytotoxic agent.

COMMENT.- This level of hyperuricaemia may well have produced acute renal failure and suggests significant tumour breakdown.

CASE NO.- 25 INITIALS.- E.C. SEX.- M AGE.- 71

DIAGNOSIS.- Inoperable carcinoma of stomach.

HISTORY.- Pain in left iliac fossa, increasing anorexia, and excessive oral flatulence for 2 weeks. Palliative gastro-enterostomy 1/3/65 for extensive carcinoma of stomach.

CYTOTOXIC TREATMENT.- Thiocolciran, 140 mg, by I.V.I. and methotrexate, 230 mg, orally. Treatment continuing.

PROGRESS.- Pain-free, eating normally, feeling well.

POINTS OF INTEREST.- Advanced carcinoma of stomach with brief history. α_2-globulin and uric acid normal initially. Slight increase in α_2-globulin 1 week after commencing therapy but no significant change in uric acid level. Urine uric acid raised initially, subsequently falling to normal levels.

COMMENT/

COMMENT.- Further records required in this case, but probably no objective effect on tumour.

CASE NO.- 26 INITIALS.- A.W. SEX.- F AGE.- 63

DIAGNOSIS.- Carcinoma of breast. Malignant pleural effusion and skin recurrence.

HISTORY.- Stage III carcinoma right breast treated by radical mastectomy and radiotherapy, September 1963. Excision of recurrent glands right axilla, June 1964. Severe herpes zoster left 10th nerve distribution, September 1963.

Increasing breathlessness, tightness in left chest, and pain in left 10th nerve distribution for 3 weeks. Large left pleural effusion proved by cytology to be of malignant origin.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 1,200 mg, by intrapleural instillation. Treatment continues.

PROGRESS.- Symptomatic relief from breathlessness but left-sided chest pain persists.

POINTS/

POINTS OF INTEREST.- Patient with uncontrolled malignant disease of breast of slow progress. α-2-globulin raised initially (no results available for 2 years previously). Level subsequently recorded as normal on 2 occasions and again being raised slightly one month after commencing treatment. Uric acid within normal limits and level unchanged by treatment. No estimation of urine uric acid levels.

COMMENT.- Tumour showing no evidence of objective response.

CASE NO.- 27 INITIALS.- J.W. SEX.- M AGE.- 66

DIAGNOSIS.- Hypernephroma, right kidney.

HISTORY.- Four months intermittent nausea, vomiting, diarrhoea and loss of 1 st in weight. One episode of mild haematuria 2 weeks previously.

Clinically, enormous mass in right abdomen shown radiologically to be an extensive hypernephroma of right kidney.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 3,600 mg, by direct intra-arterial infusion right kidney, and intravenous injection. Treatment continued.

PROGRESS/

PROGRESS.- Rapid subsidence of nausea, vomiting and diarrhoea with return of appetite and gain in weight. Abdominal mass essentially unchanged.

POINTS OF INTEREST.- Advanced hypernephroma presenting with gastro-intestinal symptoms. α-2-globulin slightly raised and serum uric acid considerably raised when first presented. α-2-globulin and uric acid levels remaining high with small peaks in uric acid levels corresponding to intermittent intra-arterial injections. This patient demonstrated a high concentration of uric acid in the urine with a marked increase following the first exhibition of cytotoxic agent.

COMMENT.- Suggests a possible objective as well as subjective response.

CASE NO.- 28 INITIALS.- R.G. SEX.- M AGE.- 59

DIAGNOSIS.- Carcinoma of colon.

HISTORY.- Colicky lower abdominal pain, increasing anorexia and weight loss for 3 months; vomiting and diarrhoea for 2 weeks.

Advanced carcinoma of transverse colon with involvement of small bowel and anterior abdominal wall at laparotomy 17/3/65. Palliative resection.

CYTOTOXIC/

CYTOTOXIC TREATMENT.- Thiocolciran, 210 mg, intravenously; and methotrexate, 190 mg, orally. Treatment continues.

POINTS OF INTEREST.- Electrophoretic pattern normal when first seen and remaining so. Serum uric acid normal initially, becoming high-normal after initiating treatment. Urine uric acid high initially with slight rise following treatment.

COMMENT.- Advanced tumour without change in protein pattern. Early uric acid results suggest possible tumour effect.

CASE NO.- 29 INITIALS.- P.D. SEX.- M AGE.- 63

DIAGNOSIS.- Carcinoma of stomach.

HISTORY.- 8-year history of dyspepsia considered on X-ray and oesophagoscopy to be due to peptic oesophagitis.

Increasing dyspepsia for 1 week culminating in a severe haematemesis.

Inoperable carcinoma of stomach at thoraco-laparotomy on 7/4/65.

CYTOTOXIC TREATMENT.- Thiocolciran, 90 mg, by intravenous injection; and methotrexate, 50 mg, orally. Treatment continues.

PROGRESS/

PROGRESS.- Eating moderately well; no pain at present.

POINTS OF INTEREST.- Advanced carcinoma of stomach long regarded as peptic oesophagitis although under repeated review. Also found to have duodenal ulcer. α-2-globulin slightly raised and remaining so to date. Uric acid normal throughout. Urine uric acid estimations not carried out.

COMMENT.- Remains under treatment and requires further results.

CASE NO.- 30 INITIALS.- J.M. SEX.- M AGE.- 61

DIAGNOSIS.- Carcinoma of bronchus.

HISTORY.- 3-month history of intermittent haematuria associated with marked weight loss, progressive dyspnoea, listlessness and lethargy. Marked ankle swelling for 1 week.

Radiotherapy for carcinoma of maxillary antrum, June 1963.

CYTOTOXIC TREATMENT.- Cyclophosphamide, 1,400 mg, by intra-arterial and intravenous injection.

PROGRESS.- Patient demonstrated widespread malignant disease with superimposed chest infection. Progressive decline to death on 17/4/65.

POINTS/

POINTS OF INTEREST.- Carcinoma of bronchus, probably presenting with secondary in maxillary antrum as first evidence and subsequently presenting as "a typical left-sided hypernephroma". α-2-globulin not raised at any stage. Uric acid initially normal. Moderate increase following initial burst of therapy, subsequently returning to normal levels. No estimation of urine uric acids.

COMMENT.- Period of assessment too short but uric acid levels suggest a possible effect on tumour breakdown.

(b) Control patients

I have not considered it necessary to detail the individual case histories of the patients included in the control group (Group B).

The disease conditions from which they suffered, the treatment they underwent, and the patterns of α-2-globulin, serum and urine uric acid are as detailed in Tables 8-10.

It is sufficient to say that the diagnosis in each case was established by accepted means, and in those cases in which there was any possibility of malignant change this has been excluded by histological examination.

VI RESULTS

The results of the study are as detailed in Tables 1-10 Tables 1-7 summarise the results of the treated patients (Group A) and Tables 8-10 summarise the results in the control group (Group B). It is considered that these tables are sufficient explanation in themselves but points of interest will be elaborated in the Discussion.

VII ASSESSMENT OF RESULTS

In assessing the results obtained a number of factors must be taken into consideration.

A total of 33 patients were introduced into the programme but of these 3 could not be assessed. In one case the patient was admitted at an early stage to another hospital and his progress could not be personally supervised. A second patient was irregular and infrequent in attendance and no worthwhile series of results was obtained. The third patient was withdrawn because of the severe side effects resulting from the first two days of cytotoxic treatment.

A total of 30 patients with advanced malignancy was therefore studied (Group A). Within this group the overall coverage of results is satisfactory but in four cases, still under treatment, insufficient results are available, and two cases are included entirely/

entirely on the grounds of unusual interest despite the results obtained being strictly inadequate.

Thirty-one patients suffering from various forms of inflammatory disease were studied as controls (Group B). All of these cases were in-patients or at convalescent centres.

The problem of out-patient investigation and assessment in the treated group proved one of considerable magnitude. Although many of these patients were able to continue frequent attendance, others were prevented from doing so by virtue of distance, lack of transport, or stage of disease. On occasion the patients were visited in nursing homes or in other units, but no attempt was made to employ the help of general practitioners on the basis that such an imposition was unjustified.

It is important to record that the number of patients with advanced malignant disease treated with cytotoxins and included in this programme, does not represent the total number of cases with advanced disease seen during the course of 12 months.

It was not considered ethical to exhibit cytotoxins in a certain number of cases that were already too advanced at diagnosis and in whom there appeared no possibility of palliation. Altogether, 8 patients came into this category and all died in the ward or at home within a short time of diagnosis.

All/

All patients with localised, surgically-treatable malignant disease have been excluded from this phase of the study.

Since there appears to be no previous study of this kind the intervals of assessment following cytotoxic therapy (or operation) have been selected somewhat arbitrarily.

Observations in the large group of patients referred to in the introduction (92 cases of malignant disease of various types treated with cytotoxins) suggested that any change recorded occurred most commonly within the first few weeks after exhibition of cytotoxins or within one week of operative manipulation. This would appear analogous to the accepted work on the metabolic response to injury in surgical operations.

Estimations were therefore carried out in both groups within 24-72 hours of starting treatment or of an operation and again within 4-7 days of commencing treatment or carrying out surgery. In the treated patients further estimations were carried out at intervals of 2 weeks, 1 month, 2 months, 3 months and 6 months.

For the reasons already given above, this ideal and intended pattern could not be followed in every case. In a few cases, however, almost daily estimations were possible, and particular significance may be given to the results obtained in these cases.

The/

The fact that many patients died in their homes precluded the possibility of carrying out autopsy in all but 4 of the 17 cases who died during the course of the programme. In all treated cases, however, the diagnosis was confirmed histologically with the exception of one case. This patient with clinical and radiological evidence of a hypernephroma remains under treatment and no biopsy has been obtained to date. One patient, W.E. aged 81, was treated with cytotoxic agents for 8 months before positive biopsy was obtained by oesophagoscopy. It is to be further noted that in this patient earlier attempts at biopsy via an oesophagoscope had resulted in a report of inflammatory tissue only.

Finally, it must be pointed out that it was initially planned to incorporate a third group of patients with non-inflammatory conditions, e.g. hernia, to act as normal controls. Reference to the literature[2,5] and consultations with the University biochemists, however, suggested that the normal values of the serum electrophoretic pattern and the serum uric acid were sufficiently well established within a laboratory complex to allow the normal values and normal ranges in daily use to be employed. This was obviously a very considerable factor in time saving but is accepted as a significant omission (Table 1).

VIII DISCUSSION/

VIII DISCUSSION

Significance of changes in α-2-globulin

The exact origin of the plasma globulins is uncertain but they are believed to be widely formed in the body by the reticuloendothelial system, the plasma cells, and the lymphoid nodules.[8]

The α-2-globulin fraction of the serum electrophoretic pattern is not a single substance but a number of closely related proteins, including certain glyco- and lipoproteins migrating between albumen and β-globulins, and only separated artificially from α-1-globulins by electrophoresis. Nevertheless, the α-2-globulin fraction behaves sufficiently as a single unit to allow of assessment under the circumstances of this study.

Very little appears to be known concerning the factors which affect the level of α-2-globulin in the plasma. The presence of an elevated α-2-globulin has been dismissed by certain authors as due to increased tissue necrosis in inflammatory and neoplastic conditions. Although this may, to some extent, be true it would appear likely from the results obtained that a raised α-2-globulin is not necessarily a concomitant of even severe inflammatory change (with necrosis) while a raised level/

level is a very common finding in malignant disease. It is tempting therefore to consider that a raised α-2-globulin in these cases is in some way related to the presence or activity of a malignant lesion. Whether or not the actual level of the α-2-globulin is of any significance is not known.

Brackenbridge (1964) has shown that there is a high correlation between α-1 and α-2 globulins and between other fractions of the serum proteins in certain diseases[9] but no definite significance is attached to changes in protein pattern.

Although the α-2 fraction was raised in 22 of the 30 cases studied (73%) the findings of a raised level in 8 of the 31 control patients (25%) with inflammatory disease confirms that this is not a finding specific to malignant disease.[10] It must be accepted that the α-2-globulin fraction is probably raised in a variety of disease conditions, but I do not concede to Petermann's view that the finding of a raised α-2-globulin level is of no diagnostic significance in malignant disease.[11]

An elevation in the level of α-2-globulin occurs with sufficient frequency to at least warrant the suspicion of malignancy in many cases, and particularly where other signs of inflammation are absent. A raised level is probably also of some value in the diagnosis of metastatic spread at a stage before this becomes clinically manifest.

The/

The concept of cancer as a systemic disease from the outset is accepted and the frequency with which changes occur in a metabolic field such as represented by the α-2-globulin gives further support to this view. It is suggested that a raised α-2-globulin in malignant disease may represent a feature of tumour-host relationship and occur as a reaction to the presence of a neoplasm.

The value of a raised α-2-globulin level as a prognostic guide in the treatment of malignant disease is a problem requiring particular thought. If a high initial level is accepted as in some way related to the presence or activity of a malignant lesion then a persistently high level, despite treatment would suggest continued activity of the neoplasm. A normal level initially and a level remaining normal throughout is more difficult to interpret. A possible interpretation is that the tumour activity in these cases is extremely slow, the breakdown of tumour is minimal and that the tumour-host resistance is undisturbed.

If the level of α-2-globulin is initially high and falls following treatment it suggests diminishing activity and breakdown of tumour and possibly a correction of the disturbed tumour-host relationship. An initial low level which subsequently rises would on this basis suggest increased activity of the tumour or recrudescence of a previously controlled tumour.

It is interesting to note that in the 10 cases demonstrating objective response as judged by changes in the α-2-globulin and uric acid levels the above pattern is approximately followed. In those cases in which a prolonged subjective response occurs, e.g. E.L., Case no. 14, the α-2-globulin level falls in parallel with the subjective response. This, I regard, as further evidence of the α-2-globulin level reflecting a more intimate relationship between host tissues and tumour than has previously been accepted and evidence against the belief that a raised α-2 level simply implies necrosis. Under these circumstances necrosis should be maximal with maximal effect of the cytotoxic drug.

I would therefore regard the significance of the α-2 level in the assessment of response to cytotoxic drug to lie in the reflection of altered tumour activity and to be less important in assessment of tumour breakdown.

Significance of changes in uric acid levels in blood and urine

Uric acid derives normally from the breakdown of purine bases in the liver. Uric acid is a normal constituent of the plasma in a level of 3.7 mg/100 ml with a range of 1.5-5 mg/100 ml in our laboratories. It is excreted by the kidneys and appears in the urine in a concentration of 100-500 mg/day on a normal diet but/

but may rise to levels of 2,000 mg/day with a diet containing a high amount of purine.[12] It is estimated that the normal ward diet contains only a moderate amount of purine and the normal range of uric acid excretion of in-patients has been calculated to lie within the range 100-750 mg/day.

Higher concentrations of uric acid in the blood and urine are found in gout, uraemia and leukaemia. In the absence of gout, uraemia or active liver disease any increase in uric acid levels in the plasma or urine may reasonable be assumed to reflect excessive purine breakdown in malignant or inflammatory tissue.

An elevation in the level of uric acid in the plasma or urine may follow the administration of cytotoxic drugs or operative manipulation. This may be regarded as further indirect evidence of tumour or tissue breakdown. Any changes in the urine uric acid excretion would be expected to approximately parallel changes in the plasma levels. In the cases in which it has been possible to estimate urine uric acid levels this has been found to be so. The cases in which this estimation was carried out, however, are too few to allow of significant conclusions.

One interesting point which has emerged from this study of uric acid levels in malignant disease, following cytotoxic therapy, is the possible relationship between malignant disease and gout. The/

The link appears to be in the breakdown of purine bases to form uric acid with resultant severe pain. Thus, the pain of gout is one of its particular features. This pain may be dramatically relieved by an antimitotic agent, colchicine, which inhibits purine synthesis. Colchicine is known to have some activity against tumour tissues. Recently we have employed the substance thiocolciran, a combination of an ethenylamine and colchicine, which has been shown to have a marked anti-tumour activity.[13] One of the striking features of the use of this drug is the severe pain which the patient experiences at the site of tumour within 3-5 hours of the injection of even a small dose of the drug. On occasions, the pain has been sufficiently severe to require the use of pethidine and its time relationships are almost predictable. It can equally be shown that certain of these patients demonstrating post-injection pain have a raised uric acid initially or a rise in the uric acid levels in plasma and urine following administration of this drug. It is possible therefore that the mobilisation of uric acid is in some way responsible for the pain in this tumour as it probably is in gout.

Remarkably little is known concerning the factors responsible for fluctuations in uric acid in human blood. There is little doubt, however, that a raised level reflects breakdown of tissue and it is my impression from this study that the uric acid levels are a better guide to the breakdown of tumour tissue than the

α-2-globulin levels which are perhaps more important in ascertaining activity of tumours.

As with α-2-globulin, four main patterns are evident in the serum uric acid levels in both treated and control patients (see Table 9). A level which is normal initially and remains normal throughout is presumed to imply minimal tumour breakdown and no appreciable effect of the drug. A high initial level which remains high throughout treatment is accepted as evidence of active tumour breakdown, occurring independently of treatment, with probably only minimal increase in breakdown when drugs are exhibited. An initially normal level, which rises following treatment, is assumed to imply breakdown of tumour tissue as a result of the drug. A raised level initially which falls following treatment possibly implies reduced breakdown by the body, no appreciable effect on breakdown from the drugs, but is consistent with slowing of activity of the tumour.

The fact that uric acid levels were elevated in the plasma of 4 of 31 control patients and in the urine of 1 of the 6 control patients in whom this estimation was carried out, is accepted as evidence of considerable and rapid tissue destruction. It is important to note that in 2 cases demonstrating a high uric acid level in the plasma there was a severe degree of liver infection and one of these cases demonstrated a frank liver abscess.

Effect of hepatic metastases on levels of α-2-globulin and uric acid

It may be argued that changing levels of α-2-globulin or uric acid in cases of malignant disease before or after treatment merely reflect the presence and extent of hepatic metastases.

Nine cases in this study were known or suspected to have hepatic metastases. It can be seen from the analyses of these 9 cases, as detailed in Table 6, that no definite relationship exists between the presence of metastases and changes in the levels of α-2-globulin or uric acid. Furthermore, in 17 patients demonstrating altered levels of α-2-globulin and/or serum uric acid, there was no evidence of hepatic metastases.

Objective assessment of tumour response at an early stage in treatment

The usual and accepted means of determining tumour response leave much to be desired. Subjective response, as judged by decrease in pain, improved wellbeing, increase in appetite or weight, may not be paralleled by objective reduction in tumour size or activity. Subjective improvement is often delayed in its appearance and indeed may not appear before the patient has suffered considerable discomfort from the side effects of cytotoxic therapy (or radiotherapy), which subsequently proves to be of very little benefit. Symptomatic improvement is also subject/

subject to considerable bias both on the part of the patient and on that of his medical attendant; any improvement obtained may be entirely unrelated to the treatment. The serial measurement of changes in tumour size by X-ray examination is seldom exact and in the several cases in which we have employed this technique the interpretation of the X-ray findings has been extremely difficult.

Assessment of response to treatment by frequent observation of a tumour, as, for example, by means of a sigmoidoscope or gastroscope, is so inaccurate, even in the hands of a single observer, that its employment is seldom worthwhile.

Since many of the cytotoxic drugs employed are exceedingly severe in their effects on normal tissues and potentially lethal if employed for too long or in too great a dose, the value of an accurate objective measurement of effect at an early stage in treatment is obvious. If it were possible to say early in the course of treatment that a particular drug was or was not being effective then a potentially costly and hazardous treatment could be stopped if no response was evident, or continued if the early results were favourable.

It is seen from Table 5 that in 8 cases showing objective response, as judged by the α_2-globulin and the uric acid levels, there is a close correlation with subjective response. Further, this response was evident in 7 of the 8 cases within 2 weeks of starting treatment. In no case showing subjective improvement without/

without objective evidence of response, as judged by changing levels of α-2-globulin or uric acid, was the improvement maintained for more than a few weeks. Conversely, 5 of the 6 cases showing prolonged symptomatic relief demonstrated objective response at some stage in their treatment. Four cases demonstrating an objective improvement, as judged by changing levels of α-2-globulin and uric acid died within 2 months of commencing treatment and are therefore excluded from the group showing subjective and objective improvement. In 2 of these 4 cases definite symptomatic improvement did occur but was short-lived. One patient demonstrated severe side effects of treatment and this probably contributed to his early death. One patient remained ill throughout with severe intercurrent infection.

Although the numbers involved are small and the total period of the study short, it is my impression that the serial estimation of uric acid levels in plasma and blood is of considerable value in assessing response to cytotoxic treatment, at least in a selected group of patients with advanced malignant disease. Furthermore, this assessment can be made in the majority of cases within 2 weeks of starting treatment, while the final results accord closely with the experience of other workers on the overall results of treating advanced cancer with cytotoxic drugs.

IX SUMMARY/

IX SUMMARY

The α_2-globulin fraction of the serum electrophoretic pattern, the serum uric acid level and the urine uric acid level were estimated in a group of 30 patients (Group A) demonstrating advanced malignant disease before, and at intervals after treatment with cytotoxic drugs. The same factors were estimated in a group of 31 control patients (Group B) demonstrating significant degrees of inflammatory disease before and at intervals after operation.

The results obtained in this study are detailed and their possible significance discussed.

The α_2-globulin fraction of the serum electrophoretic pattern was initially raised in 22 of the 30 patients (73%) with locally advanced or metastatic malignant disease and compared with an elevated level in 8 of 31 cases (25%) demonstrating severe inflammatory disease. Although a non-specific finding in malignant disease the occurrence of a raised α_2 level should arouse suspicion in a difficult or doubtful case and may be an early guide to the presence of overt metastases or to their development.

It is considered that the α_2-globulin level is a possible guide to tumour activity following treatment with cytotoxic drugs.

Serum/

Serum uric acid levels were initially raised in 10 of the 30 treated patients (Group A) as compared with 4 of 31 cases in the control group (Group B). The urine uric acid was elevated initially in 4 of the 13 treated patients in which this estimation was carried out but in only 1 of the 6 control patients. Changing levels of uric acid in the serum occurred in 8 of the 30 patients in Group A, following cytotoxic treatment, and in only 1 of the 31 patients in Group B following surgical manipulation. Changes in the urine uric acid level in the treated group occurred on 5 occasions in the 13 patients studied and again on 1 occasion in the 6 estimations among the control group.

The number of estimations of urine uric acid are insufficient to draw any significant conclusions.

It is considered that the changes in the serum uric acid following cytotoxic treatment of advanced malignant disease may be a valuable objective means of assessing tumour response. Furthermore, this assessment may be made within 2 weeks of commencing treatment in those cases in which a response is likely to occur.

The assessment of objective tumour response, as determined by a combined study of α-2-globulin and serum uric acid levels following cytotoxic therapy, produces close correlation with the subsequent/

subsequent clinical course of the treated patients and significant subjective improvement is unlikely to occur without corresponding changes in these levels.

Serial estimation of these levels as a routine following the employment of cytotoxic drugs may, therefore, be a valuable means of assessing the likely outcome of treatment and will determine, at an early stage, the small percentage of patients with solid tumours likely to be improved by continued treatment.

It is felt that these results justify an extension of the study.

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13/

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TABLE 1

NORMAL VALUES OF α-2-GLOBULIN, SERUM AND URINE URIC ACID

Protein concentrations

	Total protein	Albumin	α-1-globulin	α-2-globulin	β-globulin	γ-globulin
1	7.14 $\pm$ 0.33	3.65 $\pm$ 0.31	0.42 $\pm$ 0.10	0.67 $\pm$ 0.12	0.91 $\pm$ 0.13	1.53 $\pm$ 0.18
2	-	51.6%-68.1%	1.4%-3.3%	6.3%-13.7%	8%-16%	9.5%-21.9%

1 = after Sunderman 1964 : results = mean $\pm$ standard deviation.

2 = after Albert Recht 1959 : results = "x" + 2 x standard deviation.

Serum uric acid

Mean value = 3.7 mg/100 ml †

Range = 1.0-5 mg/100 ml †

Urine uric acid

100-500 mg/24 hours : normal diet †

100-2,000 mg/24 hours : high purine diet †

100-750 mg/24 hours : calculated ward diet

† after Jamieson and Kay, 1965.

TABLE 2

GROUP A: TREATED PATIENTS

Nature of disease	No. of cases
Cerebral astrocytoma	2
Carcinoma of breast	4
" " bronchus	2
" " colon	2
" " kidney	3
" " ovaries	2
" " pancreas	4
" " stomach	9
Carcinoma: primary unknown	2
TOTAL	30

TABLE 3

CYTOTOXIC AGENTS

Agent	Abbreviation	No. of cases in which used
Cyclophosphamide	C.P.	16
Epodyl	E	2
Methotrexate	M	13
Nitrogen mustard	HN_2	1
Thiocolciran	T.C.	15
Thiotepa	T.T.	4

N.B. (1) 12 patients were treated with one agent only.

(2) 18 patients were treated with two or more agents, separately or in combination.

TABLE 4

GROUP A: TREATED PATIENTS

α-2-globulin, and uric acid levels

	α-2-globulin		Serum uric acid		Urine uric acid	
	No.	%	No.	%	No.	%
Normal initially	8	27	20	67	9	70
Raised initially	22	73	10	33	4	30
Remaining normal	5	17	17	57	4	30
Remaining raised	17	57	6	20	3	23
Changing patterns	8	27	7	23	6	47

N.B. Urine uric acid levels determined in 13 cases only.

TABLE 5

GROUP A PATIENTS: RESPONSE TO TREATMENT

Nature of response*	No. of cases	Percentage
Subjective response only	5	17
Objective response only	4	13
Objective and subjective response	8	27
No appreciable response (or period of assessment too short)	13	43

*

(a) Subjective response : symptomatic improvement maintained for minimum period of 8 weeks.

(b) Objective response : definite changes in α-2-globulin and/or uric acid levels at some stage during treatment.

(c) Objective and subjective response : combination of (a) and (b) above.

(d) No appreciable response : no symptomatic improvement or improvement maintained for less than 8 weeks.

: no change or minimal change in α-2-globulin and/or uric acid levels during treatment.

: too short a period of assessment.

TABLE 6

GROUP A : TREATED PATIENTS : 30

EFFECT OF HEPATIC METASTASES ON LEVELS OF α-2-GLOBULIN AND URIC ACID

No. with hepatic metastases	=	9
No. demonstrating changes in α-2-globulin level	=	2
No. demonstrating changes in serum uric acid level	=	1
No. demonstrating changes in both α-2-globulin and serum uric acid level	=	4
No. demonstrating no change	=	3

N.B. In 17 patients demonstrating changes in α-2-globulin and/or serum uric acid levels there was no evidence of hepatic metastases.

GROUP A : TREATED PATIENTS

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							$\alpha 1$		$\alpha 2$		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
W.S.	Hyper-	T.C.	1964														
M	nephroma	40 mg IVI	5/3														61
60	No	between	12/3	6.6	3.6	55	0.6	8	1.0	16	0.8	12	0.7	11	-	-	20
	hepatic	15/3/64 &	16/3	7.0	3.7	52	0.3	4	1.0	14	0.8	12	1.3	18	-	-	24
1.	metastases	6/4/64	6/4	6.8	3.4	50	0.5	7	1.0	15	0.8	12	1.2	17	-	-	18
Alive																	
J.W.	Hyper-	C.P.	1965														
M	nephroma	3,600 mg	11/3														44
66	No hepatic	intra-	13/3	5.6	2.5	45	No quantitative assessment. "$\alpha 2$ & γ globulins slightly raised"								8.4	2,300	40
	metastases	arterial & by IVI	17/3	5.6	2.4	44	"	"		"	"$\alpha 2$ globulins raised"				8.2	1,800	-
		between 15/3/65 & to date	18/3												7.9	-	21
			22/3												7.5	1,800	17
19.			24/3	5.8	2.6	43	"	"		"	"$\alpha 2$ globulins raised"				6.1	-	17
			26/3												7.9	800	28
			13/4												6.9	-	35
Alive			15/4	5.7	1.8	32	0.5	9	1.0	17	1.0	17	1.4	25	8.6	1400	37
J.M.	Carcinoid	Thiotepa	1964 25/2	5.6	No quantitative assessment. "Normal electrophoretic pattern"										-	-	50
M	syndrome	75 mg by	5/3	5.0	"		"		"		"Slight increase in β globulin"				-	-	83
40	Gross	I.A.I. on	14/4	5.1	1.9	38	0.6	12	0.8	15	0.8	15	1.0	20	25.5	-	90
Died 14/4/65	hepatic metastases	12/4/65															

24.

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							$\alpha 1$		$\alpha 2$		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
A.M. M. 55	Ca. Stomach Hepatic metastases	T.C. 650mg. I.V.I.	17/3/64	7.0	4.4	62	0.3	4	0.6	9	0.8	11	1.0	14	3.3	-	10
		M 505 mg. orally between 17/3/64 & 24/4/64	13/6/64	6.1	3.5	57	0.3	5	0.7	11	0.7	12	0.9	15	3.2	-	12
			13/7/64												-	-	37
Died 19/11/64		C.P. 1200 mg. I.V.I. between 29/10/64& 5/11/64	20/8/64												-	-	38
			29/10/64	6.0	2.5	41	0.4	6	1.0	17	0.9	15	1.3	21	3.3	-	30
3.			31/10/64	6.0	2.4	40	0.4	6	1.1	18	0.9	15	1.2	20	3.6	-	44
J.MacA. F. 60	Ca. Ovaries No hepatic metastases	T.C. 380 mg. I.V.I.	18/5/64	6.0	2.6	44	0.6	10	0.8	12	0.9	14	1.2	20	6.0	-	40
		Thiotepa 22.5 mg. intra-pleural	1/6/64	6.0	2.4	40	0.7	11	0.8	12	0.9	13	1.3	24	6.2	-	45
Died 1/11/64		C.P. 600 mg. orally between 19/5/64 & 30/8/64	29/6/64														41
			13/8/64	5.8	2.7	47	0.2	4	0.7	12	0.5	9	1.6	28	5.5	-	62
4.			24/8/64														82

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
J.C. M 58 7. Died 25/8/64	Hyper-nephroma Liver metastases	C.P. 7,200 mg I.V. and orally between 20/6/64 & 25/8/64	1964 15/6 27/6 6/7 20/7 27/7	6.6 6.4 6.6 6.1	2.4 2.4 2.6 2.2	37 36 38 36	0.6 0.5 0.6 0.5	9 7 8 9	1.2 1.2 1.3 1.0	18 19 19 17	0.9 0.8 0.9 0.9	13 15 14 14	1.5 1.4 1.4 1.5	23 22 22 24	8.8 3.8 3.9 3.1	2,400 2,100 1,000 -	130 102 120 105 105
M.H. F 58 9. Died 10/7/64	Ca.colon No hepatic metastases	T.C. 60 mg I.V.M. 10 mg orally between 8/7/64 & 10/7/64	1964 1/7 9/7 10/7	6.0 6.0	2.7 2.6	45 44	0.6 0.6	10 10	1.4 1.4	23 23	0.7 0.6	11 10	0.7 0.8	11 12	3.4 3.9		85 93 97
J.G. F 53 20. Died	Ca. pancreas Hepatic metastases	C.P. 1200 mg by I.V. drip 20/1/65 21/1/65	1965 19/1 22/1 23/1 29/1 22/2	6.3 5.6 5.9 6.0	3.2 2.6 2.4 2.7	51 47 41 45	0.7 0.5 0.6 0.6	11 9 11 10	1.1 1.1 1.4 1.4	18 19 23 22	0.8 0.7 0.8 0.8	13 13 14 14	0.4 0.7 0.6 0.7	7 12 11 12	2.8 3.4 3.7 3.8	900 1100 800 -	12 17 17 20 24
S.O. F 62 10. Alive	Ca.breast No hepatic metastases	T.T. 45mg intra-pleural between 28/8/64 & 8/10/64	1964 22/7 18/9 5/10 3/12 12/4	5.4 5.6 5.6 5.6	2.2 2.7 2.6 2.6	40 49 48 48	0.4 0.3 0.4 0.3	8 6 7 6	0.9 0.9 0.9 0.7	16 16 16 13	0.9 0.7 0.8 0.8	17 13 15 15	1.0 0.9 0.9 1.0	18 16 16 19	2.9 3.0 3.4 3.2	- - - - -	41 50 27 30 20

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
M.O.	Ca. Breast	C.P. 1400 mg. by I.V. drip Started 14/1/65	1964														
F			29. 5	7.2	3.6	50	0.4	6	1.2	16	0.9	12	1.2	16	-	-	72
44	Hepatic metastases		4. 6	5.7	2.1	36	0.5	8	1.2	21	0.9	16	1.1	19	-	-	36
Died 2/2/65			1965														
			13. 1	7.0	3.2	45	0.6	9	1.6	23	0.8	12	0.8	11	7.4	-	35
			18. 1	6.5	2.5	38	0.8	12	1.6	25	0.8	13	0.8	12	6.8	-	32
5.			25. 1	6.2	2.4	38	0.8	13	1.5	23	0.8	13	0.8	13	7.0	-	37
E.L.	Ca. Pancreas	C.P. 12,550 mg. by I.V.I. & orally between 7.12.64 & 15.4.65	1964														
F			21.11	6.2	2.2	35	0.6	9	1.0	16	0.7	12	1.7	28	-	-	48
48	No hepatic metastases		28.11														30
			7.12	6.4	2.2	33	0.8	12	1.0	15	0.7	11	1.8	25	4.7	800	42
Alive			14.12	6.3	2.3	32	0.8	12	1.0	15	0.7	11	1.8	25	4.2		47
			1965														
			21. 1	7.4	2.7	36	0.7	10	0.8	11	0.9	12	2.3	31	3.8	1100	58
			18. 2	6.4	-	No quantitative assessment - Raised γ globulin									3.9		67
14.			11. 3												4.6	820	62
			15. 4	6.8	2.3	34	0.7	10	1.0	15	1.1	16	1.7	25	4.7		62
T.H.	Ca. Stomach	T.C. 350 mg. I.V.I. and M 390 mg. orally between 18.10.64 & 4.1.65	1964														
M			12.10														61
58	No hepatic metastases		14.10	6.9	3.0	44	0.7	10	1.2	18	0.6	9	1.3	19	7.7		54
			21.10	6.8	3.0	43	0.7	10	1.3	19	0.7	10	1.3	18	7.3		42
Died 15/1/65			28.10	6.9	3.0	44	0.7	10	1.3	18	0.7	10	1.3	19	7.0		75
			30.11	6.0	2.4	40	0.7	12	1.2	20	0.7	10	1.1	18	6.8		95
13.			21.12	6.1	2.4	40	0.8	13	1.2	20	0.6	9	1.1	18	6.2		68

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
E.C. M 71	Ca. stomach. No hepatic metastases	T.C. 140 mg IVI and M. 230 mg orally between 7/3/65 & to date.	1965 6/3	6.2	2.6	43	0.6	10	1.0	17	0.8	14	0.9	16	3.2	900	34
			8/3														43
			11/3	5.9	2.6	45	No quantitative assessment. "Slightly raised α_2 globulin"								3.1	700	50
			18/3	6.2	2.5	42	"	"		"	"Raised α_2 and γ globulins"				2.9	-	45
25.			1/4														30
			15/4	6.2	2.3	37	0.7	12	1.1	18	0.9	14	1.2	19	4.2	650	30
Alive			22/4	5.4	1.6	30	0.6	11	0.7	13	1.1	20	1.4	26	3.4	-	17
P.W. M 55	Ca.stomach Hepatic metastases	T.C. 80 mg IVI + M. 100 mg orally between 7/7/64 & 27/7/64	1964 24/3	7.25	No quantitative assessment. "A normal distribution"										4.0	-	5
			10/7	7.0	"	"		"	"A normal distribution"						4.2	-	7
			24/7	6.8	3.2	48	0.6	8	0.8	13	0.8	13	1.3	18	4.8	-	42
11.			27/7	6.7	3.0	44	0.5	7	0.8	14	0.9	15	1.4	20	3.9	-	66

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							$\alpha 1$		$\alpha 2$		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
M.K. F 51	Ca.breast and ca.rectum. No hepatic metastases	C.P. 1000 mg intra-pleurally between 13/4/65 & to date. N.B. Receiving testosterone & cortisone acetate between 24/1/65 & 13/4/65	1963 14/8														18
			1964 30/9														45
			1965 21/1	6.0	2.4	40	0.5	8	0.8	13	0.9	15	1.1	19	3.5	600	86
			30/3	6.0	2.3	39	0.5	8	0.8	13	0.8	14	1.2	21	8.2		50
			1/4	6.0	No quantitative assessment. "A normal protein pattern"										9.0	2600	50
			12/4												4.4		
21.			14/4	6.0	2.7	45	0.5	8	0.8	13	0.8	14	1.2	20	11.7	1400	45
			19/4	5.4	2.2	41	0.4	8	0.9	16	0.9	17	1.0	18	13.8		48
			23/4	6.1	2.4	40	0.5	9	1.0	17	1.0	16	1.2	19	9.5	-	-
J.McI. F 54	Widespread malignant disease from unknown primary	C.P. 1,800 mg by I.V. drip & I.V.I. between 14/3/65 & 17/3/65=	1965 18/2														48
			25/2	6.7	2.5	45	0.5	7	1.0	18	1.0	18	0.8	12	4.7	1400	
			13/3	5.6	1.9	34	0.6	10	0.9	16	1.1	19	1.2	21	6.1	-	48
			16/3	5.6	No quantitative estimation. "A raised $\alpha 2$ globulin"										5.9	1900	53
			19/3	5.6	1.9	34	0.5	9	1.0	17	1.1	19	1.1	20	5.6	-	50
22.			29/3	5.8	2.0	35	0.5	8	1.1	17	1.0	16	1.3	24	4.5	1050	18
Alive			5/4	5.6	1.8	33	0.5	9	1.1	18	1.0	19	1.2	21	4.8	-	60

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							$\alpha 1$		$\alpha 2$		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
E.H. F 60	Ca.ovaries	C.P.	1964														
		2600 mg	29/6	6.0	3.5	58	0.4	7	0.9	15	0.7	11	0.5	9	4.3	-	9
		I.V.I. and	16/7	5.4	2.5	46	0.5	10	1.1	20	0.7	13	0.6	11	4.8	-	39
		300 mg intra-pleurally	20/7	5.2	2.5	49	0.5	9	0.9	17	0.7	13	0.6	12	6.0	-	40
			27/7														40
		T.T.	22/8	5.2	2.2	43	0.4	7	1.0	20	0.8	16	0.7	14	6.1	-	22
		90 mg intra-peritoneal and	4/9	5.2	2.0	38	0.5	9	1.0	20	0.7	13	1.0	19	5.9	-	31
			21/10	5.3	2.2	42	0.5	9	1.1	21	0.7	12	1.0	16	5.8	-	20
8.	No hepatic metastases	60 mg intra-pleural between 11/7/64 & 31/10/64															
Died 16/11/64																	
J.H. M 59	Astro-cytoma	E.	1964														
		5,000 mg	17/11	6.4	2.4	36	0.6	10	1.0	18	0.9	16	1.2	20	5.0	-	39
	No hepatic metastases	I.A.	21/11	6.4	2.5	37	0.6	10	1.1	19	0.8	15	1.1	19	4.7	-	23
		T.C.															
		70 mg IVI	27/11	6.2	3.0	48	0.5	8	1.0	18	0.8	13	1.0	18	4.6	-	20
		C.P.															
		700 mg orally	18/12	6.4	2.4	36	0.5	7	1.1	19	0.8	15	1.1	19	4.1	-	18
			1965														
		M.	12/1	6.6	3.6	55	0.5	7	1.0	15	0.8	12	0.7	11	4.8	-	11
16.		35 mg orally between 16/11/64 & 16/1/65															
Died end of January																	

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
M.G. F 57	Astro-cytoma Grade III No hepatic metastases	Thio-colciran 480 mg IVI Metho-trexate 320 mg orally Epodyl 7,500 mg I.A. Between 18/7/64 and 18/1/65	1964 14/7 21/7 25/8 15/10 22/10 29/10 12/11 14/12 11/1	6.2 6.4 6.0 6.4 6.2	3.0 3.4 2.7 3.5 3.0	48 52 45 54 48	0.5 0.4 0.6 0.2 0.4	8 4 10 3 7	1.0 0.9 0.9 0.9 1.0	18 16 14 14 18	0.8 0.8 0.8 0.7 0.8	13 12 12 11 13	1.0 1.1 1.2 1.2 1.1	18 17 19 18 19	4.0 3.9 3.5 4.2 4.1		20 17 12 14 16 2 7 9 9
12. Died 15/3/65																	
R.G. M 59	Ca.colon No hepatic metastases	T.C. 190 mg IVI M. orally 150 mg/ Between 26/3/65 & to date	1965 10/3 26/3 30/3 7/4 20/4	6.5 6.4 6.3	No quantitative assessment. "Normal electrophoretic pattern" " " " "Normal electrophoretic pattern" 2.7	45	0.6	11	0.8	15	0.8	15	0.7	14	4.0 5.5 5.0	960 1200 800	66 48 72 73 52
28. Alive																	
P.D. M 63	Ca.stomach Hepatic metastases	T.C. 90 mg IVI M. 50 mg orally. Between 16/4/65 & to date	1963 14/10 1965 22/3 15/4 19/4 26/4	5.0 4.9 5.2	2.0 1.9 2.0	39 38 37	0.5 0.5 0.5	10 11 10	0.9 0.9 1.0	18 18 19	0.7 0.7 0.7	15 15 15	0.8 0.9 0.8	17 18 17	3.8 4.0 4.7	- - -	60 61 106 90
29. Alive																	

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							∝1		∝2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
A.P. M 62	Ca.stomach No hepatic metastases	Thio-colciran 580 mg Metho-trexate 370 mg between 11/5/64 & to date OP	1964 10/5														30
			1/6	6.9	3.5	50%	0.3	5	1.0	15	0.8	11	1.3	19	6.0	700	20
			15/6	6.6	3.3	50%	0.5	7	1.0	15	0.9	13	1.0	15	5.3	-	25
			13/7														30
			19/11	6.8	3.6	48%	0.4	6	1.1	15	0.9	12	1.3	19	5.0	480	10
			1966 18/1														17
			21/1														
			25/1												5.2	-	54
			1965 3/3	6.5	2.4	37%	Normal electrophoretic pattern										22
G.			18/3	6.7	No quantitative assessment. "Raised ∝2 globulin & slightly raised γ globulin"										3.8	600	8
			1/4														9
Alive			15/4														5
			22/4	6.6	3.2	49%	0.5	7	1.1	16	0.8	12	1.0	15	4.0	-	3

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
A.G. M 61 Alive 17.	Ca. Stomach No hepatic metastases	T.C. 400 mg. I.V.I. M 80 mg. orally Between 20/11/64 and to date	14/11/64	6.0	2.3	38	0.6	10	1.2	19	0.8	14	1.2	19	6.2	2000	35
			19/11/64	5.9	2.2	37	0.5	9	1.2	20	0.8	14	1.2	20	7.0		65
			15/12/64	7.0	3.0	43	0.6	8	1.2	18	0.8	10	1.2	21	-		24
			21/1/65														4
			18/2/65	5.8	-	No quantitative assessment - "a normal protein pattern"									7.1	1800	90
			4/3/65	5.9	2.4	40	0.6	10	1.3	21	0.8	10	1.1	19	6.4		36
			8/4/65												6.4		38
			22/4/65	6.5	2.0	31	0.6	9	1.0	16	1.3	20	1.6	24	4.7	-	33

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α1		α2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
R.C.	Ca.stomach	T.C.	1965														
M		120 mg IVI	3/2	5.9	3.3	56	0.2	4	0.8	13	0.5	9	1.1	18	2.9	-	23
66		M.	30/3	6.6	No quantitative assessment. "Normal electrophoretic pattern"										3.0	-	15
		115 mg orally	3/4														15
23.	No hepatic	between	7/4	6.4	3.4	52	0.4	4	0.9	15	0.6	10	1.2	19	3.4		38
Alive	metastases	31/3/65 & to date	22/4	5.8	2.3	40	0.5	8	0.9	16	0.9	16	1.2	20	2.5		28
A.W.	Ca.breast	C.P.	1965														
F	No hepatic	1200 mg	10/3	6.9	3.1	45	No quantitative assessment. "Raised α2 globulin"								4.0	-	6
63	metastases	intra-	18/3	6.5			No quantitative assessment. Normal electrophoretic pattern								4.1	-	8
		pleural between															
26.		11/3/65 &	25/3	6.3			"	"		"			Normal electrophoretic pattern		4.7	-	2
		to date	12/4	6.4	3.4	52	0.4	4	0.9	16	0.8	12	1.1	17	4.5	-	8
Alive			22/4	6.4	2.6	41	0.6	9	1.0	16	1.0	15	1.2	19	3.7	-	-
W.E.	Ca.stomach	T.C.	1964														
M	No hepatic	350 mg IV	2/1	6.4	3.6	56	0.3	4	0.9	14	0.9	14	0.8	12	-	-	64
81	metastases	M.	20/1	6.1	3.4	55	0.2	4	0.8	13	0.7	12	1.0	16	-	-	-
		32.5 mg orally	3/2	6.5	3.3	51	0.3	4	1.3	20	0.7	10	1.0	15	-	-	46
2.		10/1/64-	2/5	7.3	3.8	52	0.3	4	1.0	14	0.8	11	1.4	19	-	-	10
		27/3/64 and	7/8														14
Died 15/1/65		2/5/64- 12/5/64	18/8														41

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
J.K.	Ca. Pancreas	C.P. 5650 mg. by mouth & I.V. drip between 26/11/65 &25/12/65	1964														
M			19.11	5.8	2.3	39	0.5	8	1.1	19	0.6	11	1.3	23	3.4	600	26
6	?Hepatic metastases		26.11														55
			10.12														61
Died 12/1/65			30.12	5.9	2.3	38	0.5	8	1.2	20	0.6	11	1.3	23	3.9	480	29
			1965														
15.			1.1														27
J.W.	Wide: spread malignant disease from ? broncho: genic neoplasm	HN_2 30 mg. I.V.I. C.P. 2400 mg. orally between 22.1.65 & 9.3.65	1965														
M			11.1	5.6	2.6	47	0.4	7	1.2	21	0.8	15	0.6	10	3.0	800	23
35			22.1												3.1		56
			23.1												2.8	840	-
Died 22/3/65			27.1	6.2	2.6	42	0.5	8	1.4	23	0.9	14	0.8	13	3.2		59
			29.1	6.4	3.4	53	0.7	11	1.3	21	0.5	7	0.5	8	3.0		74
19	Hepatic metastases		30.1												3.5	700	-
			1.2												2.6		-
			2.2												2.4		-
			3.2	6.9	3.2	47	0.7	10	1.6	23	1.0	14	0.4	6	2.6		75
			5.2												2.9		-
			13.2												3.0		78
			15.2	6.0	- No quantitative assessment "Raised α_2 and γ globulins"										-		76
			3.3	6.2	2.9	46	No further quantitative assessment "α_2 globulin raised"								5.2		69

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
J.T. M 59 Died 18.4.65 18.	Ca. Pancreas Gross hepatic metastases	C.P. 9400 mg. by I.V.I. orally & intra-peritoneal Between 14/12/64 & 15/4/65. Second operation 8/2/65	2/12/64														16
			14/12/64	7.0	3.0	43	0.6	8	1.2	17	0.7	9	1.1	22	6.0	780	31
			28/12/64	6.9	3.0	42	0.7	9	1.1	16	0.7	9	1.2	23	6.0		35
			21/1/65												3.1		15
			5/2/65	7.4	3.9	53	0.6	9	1.2	16	0.7	10	0.9	12	5.3	840	29
			16/2/65												8.2		47
			8/3/65	5.9	- No quantitative assessment - "raised α_2 globulin" -										-		30
			18/3/65	5.9	- No quantitative assessment - "low albumin" -										5.3	1200	60
			1/4/65	5.9	- No quantitative assessment - "raised α_2 globulin and low albumin" -										4.8		54

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							∝1		∝2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
J.M. M 62 Died 18.4.65 30.	Ca. Bronchus Wide-spread metastases	C.P. 1400 mg. by I.V.I. and intra: arterial between 2.4.65 & 8.4.65	30/3/65	5.2	2.0	38	0.6	12	0.8	16	0.8	16	0.9	18	3.7	-	53
			3/4/65												4.8	-	42
			5/4/65	5.0	1.9	37	0.5	11	0.8	17	0.8	17	0.9	18	5.0	-	46
			7/4/65												3.7	-	37
			9/4/65	4.8	1.6	33	0.5	12	0.8	18	0.8	18	0.8	18	3.3	-	35
			13/4/65	4.1	1.2	30	0.4	9	0.7	18	0.7	18	1.0	25	4.2	-	39
			15/4/65												3.9	-	12

TABLE 8

GROUP B : CONTROL PATIENTS

NATURE OF DISEASE

Nature of disease	No. of cases
Biliary tract disease	9
Ruptured aortic aneurysm	1
Diverticulitis	4
Ulcerative colitis	4
Crohn's disease	2
Peptic ulceration	6
Infection : Others	5
TOTAL	31

TABLE 9

GROUP B : CONTROL PATIENTS - 31 patients

α-2-GLOBULIN AND URIC ACID LEVELS

	α-2-globulin		Serum uric acid		Urine uric acid	
	No.	%	No.	%	No.	%
Normal initially	23	75	24	85	5	-
Raised initially	8	25	5	15	1	-
Remaining normal	20	66	24	85	5	-
Remaining raised	7	22	4	12	-	-
Changing patterns	4	12	1	3	1	-

N.B. Urine uric acid estimations in 6 cases only

GROUP B : CONTROL PATIENTS

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							∝1		∝2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
N.McD. M 35	Ulcerative colitis	Colectomy 2/6/64	1964														
			23/5	6.8	2.9	42	0.5	7	1.2	17	1.1	16	1.2	18	3.4	600	71
			3/6	6.1	2.5	41	0.4	6	1.0	17	0.9	15	1.3	21	3.8	400	16
			11/6	6.3	2.4	34	0.8	13	1.0	16	0.8	13	1.4	22	4.1	700	74
M.C. F 55	Diverti-culitis	(L) hemi-colectomy 24/7/64	1964														
			21/7	6.8	3.3	49	0.3	4	0.8	12	1.0	15	1.2	18	4.2	400	61
			25/7	6.9	3.4	50	0.3	4	0.9	13	1.0	15	1.2	18	3.8	300	40
			1/8	6.7	3.3	48	0.3	4	0.8	12	0.9	14	1.1	18	4.0	400	35
J.C. M 64	Ulcerative colitis	Caecostomy 1/9/64	1964														
			18/8	4.7	2.3	48	0.4	8	0.6	13	0.7	15	0.7	16	2.7	-	80
			2/9	4.7	2.0	45	0.4	8	0.6	13	0.7	14	1.0	22	4.0	-	63
			11/9	5.5	2.4	43	0.4	7	1.0	18	0.6	11	1.2	21	2.3	-	70
H.P. F 79	Crohn's disease Rectum	Transverse colostomy 4/9/64	1964														
			28/8	7.3	2.8	36	0.6	9	0.8	11	1.0	13	2.2	30	6.0	-	96
			6/9	6.8	3.0	43	0.7	10	0.8	12	1.1	17	1.3	18	5.0	-	80
			14/9	6.8	3.1	43	0.7	10	0.8	12	1.0	16	1.4	19	5.0	-	40
C.S. F 42	Ulcerative colitis	Colectomy 25/8/64 Drainage subphrenic abscess 3/11/64	1964														
			17/8	6.2	2.2	35	0.6	9	1.0	16	0.7	12	1.7	28	4.0	-	80
			28/8	6.2	2.1	35	0.6	9	1.0	16	0.7	12	1.6	27	3.9	-	74
			31/8	6.4	2.2	32	0.5	8	1.1	17	0.8	13	1.5	25	3.8	-	73
			14/10	6.4	2.1	33	0.6	9	1.2	19	0.8	13	1.7	26	-	-	113
G.D. M 56	Ulcerative colitis	Colectomy 6/11/64	1964														
			2/11	5.2	2.0	39	0.5	10	1.1	21	0.7	14	0.8	16	4.0	-	72
			8/11	5.3	1.7	32	0.7	13	1.1	21	0.7	13	1.1	21	3.7	-	75
			23/11	5.7	1.7	29	0.7	12	1.0	17	0.7	12	1.7	31	3.6	-	50

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
W.W. M 68	Perforated diverticulitis	Transverse colectomy 24/11/64	1964 24/11 25/11	6.0 6.0	2.3 2.1	39 37	0.5 0.5	8 8	0.8 0.8	13 13	0.8 0.9	14 15	1.2 1.2	21 21	3.0 3.2	- -	71 84
A.A. M 78	Empyema of gall-bladder Liver abscess	Antibiotics No operation 9/2/65	1965 11/2 18/2	5.4 6.0	2.2 2.3	41 39	0.4 0.4	8 7	0.8 0.8	15 14	0.9 0.9	17 16	1.1 1.2	19 19	6.4 7.6	- -	40 60
V.E. F 62	P.A. Varicose ulcer	Skin grafting 24/11/64	1964 20/10 26/11 1/12	6.8 6.7 7.1	2.8 2.9 2.8	38 40 40	0.5 0.5 0.5	7 8 7	0.8 0.8 0.8	12 12 11	1.3 1.4 1.3	18 19 17	1.4 1.4 1.7	20 20 25	4.8 4.2 4.0	200 300 200	30 28 14
F.C. M 68	Prostatism Severe urinary infection	Prostatectomy 6/12/64	1964 2/12 8/12	6.3 6.2	2.8 2.8	45 45	0.4 0.5	6 7	0.9 0.8	14 13	0.8 0.8	12 13	1.4 1.3	23 22	3.8 3.6	- -	20 14
N.F. F 57	Empyema of gall-bladder	Cholecystostomy 15/3/65	1965 4/3 16/3 20/3	5.8 5.8 5.8	1.7 1.9 1.8	30 32 32	No quantitative assessment but raised α-2 & γ-globulin 0.6 0.6	 10 10	 1.2 1.2	 20 20	 0.5 0.5	 8 8	 1.7 1.7	 30 30	9.5 8.8 6.0	800 700 850	36 34 -
J.M. M 62	Cholangitis Stone in C.B.D. Septicaemia	Choledocholithotomy 7/1/65	1964 30/12 8/1 13/1	6.0 5.5 4.3	2.5 No quantitative assessment. "Normal pattern" 1.6	43 40	0.5 0.6	8 9	0.8 1.0	14 16	0.9 0.6	16 9	1.1 1.3	19 20	6.1 6.4 3.0	- - -	80 73 60
E.B. M 68	Obstructive jaundice Chronic pancreatitis	Bypass 26/4/65	1965 20/4 27/4	6.8 6.7	2.7 2.6	39 38	0.5 0.5	8 8	1.0 1.0	14 14	0.8 0.8	12 12	1.8 1.7	27 26	5.6 6.0	- -	90 100

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
W.A. M 47	Gastric ulcer. Very high acid Severe PO complications	Gastrectomy & vagotomy 20/1/65	1965 18/1	7.1	3.2	45	0.3	4	1.0	14	0.8	11	1.8	26	4.5	-	4
			22/1	6.8	3.4	50	0.4	7	1.1	16	0.8	12	1.0	15	4.2	-	35
			1/2	6.0	2.4	40	0.6	11	1.2	20	0.7	10	1.1	18	4.0	-	60
			17/2	5.7	No quantitative assessment - low albumin - high α-2 and γ-globulin										-	-	54
J.B. F 48	Cholangitis	Choledocho lithotomy 24/5/65	1964 21/5	5.9	3.2	54	0.2	4	0.8	13	0.6	10	1.2	19	3.0	200	60
			26/5	6.0	30	50	0.3	5	0.8	13	0.7	11	1.1	18	2.8	200	18
			7/6	6.0	3.0	50	0.3	5	0.7	12	0.8	12	1.2	19	2.7	-	10
B.M. M 30	Perforated D.U.	Closure 25/5/64	1964 25/5	6.1	2.8	45	0.4	6	0.7	11	0.8	13	1.1	18	2.0	-	4
			28/5	6.0	2.8	45	0.4	6	0.8	12	0.8	12	1.2	19	2.8	-	6
B.C. M 64	Acute chole-cystitis	Chole-cystectomy 24/8/64	1964 24/8	5.9	2.8	47	0.5	7	0.8	12	0.8	12	1.0	16	4.0	400	18
			27/8	5.8	2.6	44	0.5	7	0.7	11	0.9	14	1.0	16	3.0	300	20
			29/8												3.0	300	18
J.D. M 28	Perforated D.U.	Closure 18/8/64	1964 18/8	6.4	2.2	33	0.8	12	0.8	12	1.0	15	1.6	22	3.0	-	8
			22/8	6.4	2.4	37	0.8	11	0.8	11	1.1	15	1.6	22	2.8	-	18
M.A. F 68	Perforated D.U.	Closure 17/4/64	1964 17/4	5.8	2.9	46	0.5	7	0.7	11	0.9	14	10	18	4.0	-	23
			19/4	5.4	2.7	50	0.5	8	0.7	12	0.9	15	1.1	19	3.8	-	24
			25/4	5.4	2.6	49	0.4	7	0.7	12	0.9	15	1.1	19	3.6	-	20
J.O. F 64	Diverticulitis	Transverse colostomy 20/5/65	1964 18/5	6.0	3.0	50	0.4	6	0.8	13	0.7	11	1.2	18	2.9	-	6
			24/5	6.1	2.8	47	0.5	7	0.8	13	0.9	14	1.2	18	3.6	-	18

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α1		α2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
G.U. M 22	Crohn's disease	Resection of ileum 25/6/64	1964														
			24/6	6.0	2.4	40	0.5	8	0.8	13	0.9	15	1.1	19	4.0	-	62
			27/6	6.0	2.3	39	0.5	8	0.8	13	0.9	15	1.1	19	3.8	-	48
			3/7	6.1	2.2	38	0.5	8	0.8	13	1.0	16	1.2	19	3.6	-	30
D.S. M 67	Sigmoid volvulus Malabsorption	Pelvic colon resection 27/1/65	1965														
			20/1	5.0	2.1	45	0.3	6	0.9	16	0.9	16	1.0	17	4.9	-	5
			30/1	4.8	2.0	43	No quantitative assessment. "Raised α2"								4.3	-	8
			17/2	4.5	2.1	45	"	"	"		"		"		4.8	-	12
J.H. M 78	Gangrenous loop of small bowel - Meckel's diverticulitis	Resection of loop of small bowel 2/3/65	1965														
			2/3	6.1	2.6	44	0.6	9	0.8	12	0.9	14	1.4	21	4.8	-	28
			4/3	6.0	2.7	46	0.6	9	0.8	12	1.0	16	1.1	17	4.1	-	30
			11/3	6.0	2.6	45	0.6	9	0.7	11	1.0	16	1.2	18	4.2	-	28
R.C. M 58	Diverticulitis	Resection of pelvic colon 26/2/65	1965														
			21/2	6.2	2.5	43	0.7	10	0.7	10	1.1	17	1.4	20	3.2	-	18
			28/2	5.8	2.1	36	0.5	8	0.8	12	1.2	20	1.6	24	3.1	-	10
			7/3	6.1	2.4	40	0.7	10	0.7	10	1.1	17	1.6	23	3.4	-	5

TABLE 10a

CASE SEX AGE	DIAGNOSIS	TREATMENT	DATE	TOTAL PROTEIN	ALBUMIN		GLOBULINS								SERUM URIC ACID	URINE URIC ACID	ESR
							α_1		α_2		β		γ				
				G/100ml	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	G/100ml	%	mg/100ml	mg/24hr	
J.H. M 45	Duodenal ulcer + Xmas disease	G.E. + vagotomy 26/4/65	1965 20/4	6.5	3.0	47	0.5	8	0.8	12	0.8	12	1.3	21	4.1	-	5
			27/4	6.3	2.8	46	0.5	8	0.8	11	0.8	11	1.3	23	3.8	-	5
D.S. M 69	Chole-cystitis & chole-lithiasis	Chole-cystectomy 26/4/65	1965 24/4	6.4	3.1	48	0.4	6	1.0	15	0.9	14	1.1	17	3.0	-	8
			27/4	6.3	3.0	48	0.4	6	0.9	14	0.9	14	1.1	17	2.3	-	3
M.P. M 68	Chronic pancreatitis	Bypass 9/4/65	1965 8/4	5.6	2.4	43	0.5	9	0.7	13	0.9	16	1.1	19	2.3	-	40
			11/4	5.6	2.4	43	0.4	8	0.7	13	0.9	16	1.2	20	4.0	-	38
S.M. F 56	Mucocoele of gallbladder	Chole cystectomy 10/4/65	1965 9/4	6.9	2.6	38	0.5	7	1.2	18	1.0	14	1.6	23	3. 0	-	10
			11/4	6.8	2.6	38	0.5	7	1.1	17	1.1	15	1.5	22	4.1	-	-
E.G. M 71	Ruptured aortic aneurysm	Conservative 11/4/65	1965 15/4	5.2	1.9	36	0.6	11	0.7	14	0.8	15	1.2	24	4.0	-	28
			18/4	5.3	2.0	36	0.6	11	0.7	14	0.8	15	1.3	24	3.8	-	26
			21/4	5.2	1.8	35	0.6	11	0.7	14	0.8	15	1.2	24	3.1	-	29
G.L. M 64	Chole-cystitis + diabetes	Cholecyst-ectomy 18/4/65	1964 26/10	6.0	3.1	51	0.5	8	0.9	15	0.7	11	0.9	15	3.0	-	18
			1965 19/4	5.9	2.5	43	0.5	8	0.8	14	0.9	16	1.1	19	3.1	-	14
J.F. M 66	Stomal ulcer	Excision 29/4/65	1965 27/4	5.7	2.3	41	0.4	7	0.8	14	0.9	16	1.3	22	2.8	-	3
			30/4	5.6	2.3	40	0.4	7	0.7	13	0.9	16	1.3	22	2.6	-	5